Received: 22 June 2020 | Accepted: 31 December 2020

DOI: 10.1111/crj.13325

BRIEF REPORT

WILEY

Persistence of both reversible airway obstruction and higher blood eosinophils may predict lung function decline in severe asthma

Bruno Sposato[1,2] | **Marco Scalese**[3] | **Alberto Ricci**[4] | **Paola Rogliani**[5] | **Pierluigi Paggiaro**[6] | **The Omalizumab Italian Study Group**

[1]Azienda USL Toscana Sud-Est Pneumology Department, "Misericordia" Hospital, Grosseto, Italy

[2]Experimental Medicine and Systems, Department of Systems Medicine, University of Rome "Tor Vergata", Rome, Italy

[3]Clinic Physiology Institute, National Research Centre, Pisa, Italy

[4]Division of Pneumology, Department of Clinical and Molecular Medicine, Sapienza University of Rome, AOU Sant'Andrea, Rome, Italy

[5]Respiratory Unit, department of Experimental Medicine, University of Rome "Tor Vergata", Rome, Italy

[6]Department of Surgery, Medicine, Molecular Biology and Critical Care, University of Pisa, Pisa, Italy

Correspondence
Bruno Sposato, U.O. Pneumologia, Azienda Ospedaliera "Misericordia", Via Senese 161, Grosseto 58100, Italy
Email: bru.sposato@gmail.com

Abstract

Objective: This study analysed whether the persistence of both reversible airway obstruction (RAO) and elevated BE counts was associated to reduced asthma control and accelerated lung function decline in treated severe asthmatics.

Methods: About 202 severe asthmatics were studied after 12–120 months of step-5 treatment associated to anti-IgE therapy. Following treatments, reversibility tests, after inhaling 400 mcg of Salbutamol, were performed. $FEV_1 > 12\%$ or $\leq 12\%$ changes differentiated RAO+ from RAO− subjects. Blood eosinophil (BE) counts after treatment were considered.

Results: Pre-/post-treatment bronchodilator $FEV_1\%$ and ACT were lower (61% [50–71], 74.4% [62.5–83.7] and 20[18–22]), whereas BE were higher (380 cells/μl [170–590]) in RAO+ compared to RAO− subjects (77% [64–88], $p = 0.0001$, 81.8% [66.1–94.3], $p = 0.0001$, 21[18–23], $p = 0.045$ and 230 cells/μl [80–360], $p = 0.003$). A negative relationship between SABA-induced $FEV_1\%$ changes and pre-bronchodilator $FEV_1\%$ ($\beta = -0.551\%$; $p = 0.0001$) and ACT ($\beta = -0.059$; $p = 0.038$) was found. Conversely, post-treatment BE levels were positively related ($\beta = 145.565$ cells/μl; $p = 0.003$) to $FEV_1 > 12\%$ increases. A rising trend of pre-/post-bronchodilator $FEV_1\%$ in time was observed in RAO− subjects with BE < 300 cells/μl. Conversely, we highlighted significant declining tendencies of pre/post-bronchodilator $FEV_1\%$ in RAO+ patients with BE > 300 cells/μl reaching lower values after more than 36 months of step-5 treatment (59.6% [39.9–72.1] vs 74[66.5–89.2] of RAO+ individuals with BE < 300 cells/μl [$p = 0.026$] and 81.6% [66.1–91.8] of RAO-subjects with BE > 300 cells/μl [$p = 0.009$]).

Conclusion: Persistent SABA-induced $FEV_1 > 12\%$, especially when associated to BE > 300 cells/ml, may be a marker of accelerated lung function decline in severe asthmatics despite maximal step-5 treatment. The highest bronchodilation associated to the lowest BE levels should be the main goal of asthma treatment to prevent such decline.

KEYWORDS

allergic asthma, blood eosinophil, bronchodilator reversibility, lung function decline; severe asthma; salbutamol

1 | INTRODUCTION

A positive reversibility test to salbutamol can foresee an unsuitable asthma control in regularly treated subjects.[1,2] Post-bronchodilator spirometric values may reflect patients' "personal best" results. The therapy goal is to achieve a personal best FEV_1 and consequently optimal disease control.[1] A positive bronchodilator response to short acting β2-agonists (SABA) may be associated to higher airway inflammation levels and therefore, to lower asthma control. Actually, exhaled nitric oxide (FENO), eosinophils in bronchial biopsy or a combination of serum IgE, blood eosinophils (BE) and FENO are correlated to bronchodilator responses.[3–7] Additionally, patients with greater SABA-induced FEV_1 increase showed higher sputum or blood eosinophil levels compared to subjects with lower bronchial obstruction reversibility.[6,7] Therefore, significant reversibility may reflect airway eosinophilic inflammation. Furthermore, some studies confirm that higher blood/sputum eosinophils and an elevated FENO level are associated not only with a greater airflow obstruction, but also with an enhanced lung function decline.[8–13] Actually, some asthmatics present an accelerated lung function decline. Such decline is probably a functional reflection of airway remodelling, a consequence of inflammation induced structural and functional changes in the airways due to injury and repair processes of the airway tissue.[14] As already said, some studies have shown a correlation between a greater FEV_1 decline and the elevated levels of inflammatory cells (sputum or blood eosinophils and neutrophils, bronchial CD8+ T cells) and cytokines (serum periostin, IL5 and IFN γ).[8–13]

The reversible airflow obstruction (RAO) prevalence and its relationship with asthma control are not well known in severe asthmatics under maximal step-5 treatment. It is also unclear whether RAO persistence might be linked with a constantly higher BE counts and whether both conditions can be also associated to an accelerated lung function decline in treated severe asthmatics. Therefore, we evaluated whether the persistence of both RAO and elevated BE counts was associated to reduced asthma control and accelerated lung function decline in a group of treated severe asthmatics.

2 | MATERIALS AND METHODS

We retrospectively evaluated 202 severe allergic asthmatics who had been under step-5 treatment associated with Omalizumab. Various outcomes in the last follow-up visit (performed after periods varying from 6 to 120 months of treatment) were considered. At the end of each period, FEV_1, Asthma Control Test (ACT), FENO, BE counts, medications used, possible controller therapy steps-downs, number of moderate/severe exacerbations (in the last 6–12 months), ICS doses and SABA use as needed in the last month of treatment, were considered as step-5/Omalizumab therapy responses. Following patients' treatments, spirometries with reversibility tests, after inhaling 400 mcg of Salbutamol, were performed. Using $FEV_1 > 12\%$ or $\leq 12\%$ as parameters, patients were considered affected either by RAO or non-RAO respectively. Pre- and post-bronchodilator $FEV_1\%$, at the end of patients' treatments, were evaluated in RAO and non-RAO subjects by relating them to BE counts (>300 or ≤300 cells/μl) measured after patients' therapies. Data concerning individuals enrolled for the Novelli et al study,[15] for which the protocol was approved by Pisa University Hospital's Ethics Committee, (protocol 105 FPR0001 no. 3436, approved on 10 November 2011) and for which informed consent was obtained for each patient, was used for the purpose of our study. Thus, post hoc analysis of the previous study data were performed according to the objective of our research.

3 | RESULTS

83 RAO+ ($FEV_1 > 12\%$) and 119 RAO− subjects ($FEV_1 \leq 12\%$) were identified. Pre-/post-bronchodilator $FEV_1\%$, BE counts and ACT (61% [50–71], 74.4% [62.5–83.7], 380 cells/μl [170–590] and 20[18–22]), measured after treatment periods, were worse in RAO+ subjects when compared to results of RAO− individuals (77% [64–88], $p = 0.0001$, 81.8% [66.1–94.3], $p = 0.0001$, 230 cells/μl [80–360], $p = 0.003$ and 21[18–23], $p = 0.045$; Table 1). No differences in other outcomes were observed. Multivariate analysis (adjusted for confounding factors) showed post-treatment pre-bronchodilator $FEV_1\%$ values negatively ($\beta = -0.271\%$; $p = 0.0001$) associated with $FEV_1 > 12\%$ changes after Salbutamol (compared to FEV_1 variation ≤12% subjects) (Table 2). Conversely, after treatment, BE levels were positively related ($\beta = 145.565$ cells/μl; $p = 0.003$) to $FEV_1 > 12\%$ increases. Significantly reduced ACT enhancements ($\beta = -0.059$; $p = 0.038$) per unit of $FEV_1\%$ variation after reversibility test were also found (Table 2).

Pre-bronchodilator $FEV_1\%$ measured at 12–36 (65.15% [50–71.8] and at >36 months (59% [43.5–69.8]) of step-5 asthma-guidelines treatment was lower in RAO+ in comparison to RAO− patients (pre-bronchodilator FEV_1: 77% [67.2–89.7] at 12–36 months; 79.6% [61.9–89.7] at >36 months; $p < 0.0001$). Post-bronchodilator $FEV_1\%$ (after more than 36 months) was lower in RAO+ (71.3% [60.4–83.5]) in comparison to RAO− subjects (82.3% [64.6–94.9]; $p = 0.018$), whereas no differences were found in subjects treated for less than 12 months (data not shown). A significantly increasing trend of both pre- and post-bronchodilator $FEV_1\%$ was observed in RAO− subjects with BE < 300 cells/μl, while a stable tendency in RAO− patients with BE > 300 cells/μl (Figure 1A,B) was detected. Conversely,

TABLE 1 Characteristics of RAO− (FEV1 ≤ 12%) and RAO+ (FEV1 > 12%) patients

	RAO− subjects: $FEV_1 \leq 12\%$	RAO+ subjects: $FEV_1 > 12\%$	*p*
Subjects (n) M/F	119 (58.9%) 65/54 (54.6/45.4%)	83 (41.1%) 64/19 (77.1/22.9%)	**0.001**
Age	54 [45–64]	54 [45–61]	0.705
BMI	26.9 [24–29.4]	26.4 [24.2–31]	0.700
Smokers	35 (29.4%)	18 (22%)	0.410
Months of Omalizumab therapy	33 [15–48]	29 [17–48]	0.594
Doses of Omalizumab	504.9 ± 265	523.1 ± 277.5	0.896
Sensitizations to house dust mite	89 (74.8%)	63 (75.9%)	0.945
Sensitizations to pollens	51 (42.8%)	36 (43.4%)	0.963
Sensitizations to moulds	14 (11.6%)	9 (10.8%)	0.856
Sensitizations to cat/dog dander	36 (30.4%)	25 (30.5%)	0.988
Total serum IgE (UI/ml)at baseline	301 [139–584]	378.5 [229–604.5]	0.158
Eosinophils (n° cells/μl) evaluated in 155 patients	230 [80–360]	380 [170–590]	**0.003**
Eosinophils (%) evaluated In 155 patients	4 [2–6.7]	4.6 [2.8–8.1]	0.225
FEV_1% increase after salbutamol	5 [0–8]	19 [15–24.9]	**0.0001**
FEV_1% pre-bronchodilator	77 [64–88]	61 [50–71]	**0.0001**
FEV_1% post-bronchodilator	81.8 [66.1–94.3]	74.4 [62.5–83.7]	0.009
N° of subjects with FEV_1% pre-bronchodilator > 80%	51 (42.8%)	7 (8.4%)	**0.0001**
N° of subjects with FEV_1% post-bronchodilator > 80%	70 (58.8%)	50 (60.2%)	0.918
Exacerbation number in the previous year	0 [0–1]	0 [0–1]	0.667
N° of subjects without exacerbations in the previous year	68 (59.6%)	49 (59.8%)	0.988
N° of subjects with exacerbations > once a year (in the previous year)	46 (40.4%)	33 (40.2)	
FENO (ppb)	28 [16–45]	23.5 [16–36]	0.655
Subjects with FENO > 25 ppb (%)	33 (55.9%)	16 (42.1%)	0.184
Subjects with FENO ≤ 25 ppb (%)	26 (44.1%)	22 (57.9%)	
ACT	21 [18–23]	20 [18-22]	**0.045**
Subjects with ACT ≥ 20 (%)	83 (69.7%)	47 (56.6%)	**0.055**
Subjects with ACT < 20(%)	36 (30.3%)	36 (43.4%)	
No SABA use in the previous month	68 (66.7%)	40 (54.8%)	0.111
SABA use > once in the previous month	34 (33.3%)	33 (45.2%)	
Unchanged level or step-up of therapy	64 (59.3%)	42 (55.3%)	0.589
Therapy step-downs	44 (40.7%)	34 (44.7%)	
Low dose of ICS therapy	9 (12.3%)	8 (7.8%)	0.120
Medium dose of ICS therapy	31 (42.5%)	32 (31.4%)	
High dose of ICS therapy	33 (45.2%)	62 (60.8%)	

The bold highlights the outcomes with statistical significance compared to the other non-significant ones.

we highlighted both pre- and post-bronchodilator FEV_1% declining tendencies in RAO+ patients with BE > 300 cells/μl (Figure 1C,D). In fact, post-bronchodilator FEV_1% in RAO+ patients with BE > 300 cells/μl, after more than 36 months of step-5 treatment, was lower (59.6% [39.9–72.1] than the one measured in RAO+ individuals with BE < 300 cells/μl (74% [66.5–89.2]; $p = 0.026$) and in RAO-subjects with BE > 300 cells/μl (81.6% [66.1–91.8]; $p = 0.009$). RAO+ patients with BE > 300 cells/μl, that may characterise an accelerated FEV_1 decline, were 36/155 (23.2%).

4 | DISCUSSION

About 41% of our severe asthmatics showed RAO despite a step-5 level treatment. They were characterised by lower

TABLE 2 Relationships between RAO+ patients and RAO− subjects in various outcomes measured at the end of the step 5/Omalizumab treatment period and associations among the various results and changes in FEV_1% obtained after the reversibility test to salbutamol at the end of the treatment period

Outcomes obtained after step 5/Omalizumab treatment	RAO+ subjects (with FEV_1 > 12%; n = 83) (Ref.: RAO− patients, with FEV_1 ≤ 12%; n = 119)	FEV_1% changes after reversibility test with salbutamol
FEV_1% pre-bronchodilator (β)	**−0.271 (p = 0.0001)**	**−0.551 (p = 0.0001)**
FEV_1% post-bronchodilator (β)	**0.268 (p = 0.0001)**	**0.318 (p = 0.0001)**
ACT (β)	0.199 (p = 0.762)	**−0.059 (p = 0.038)**
ACT < 20 (vs. > 20) OR [95% CI]	0.948 [0.572–1.929] (p = 0.693)	1.016 [0.979–1.054] (p = 0.403)
FENO (β)	5.591 (p = 0.601)	0.427 (p = 0.439)
FENO > 25 (vs. < 25) OR [95% CI]	1.274 [0.633–2.563] (p = 0.497)	0.967 [0.917–1.021] (p = 0.224)
BE (β)	**145.565 (p = 0.003)**	3.174 (p = 0.149)
BE% (β)	0.583 (p = 0.390)	0.012 (p = 0.664)
Exacerbations posttreatment > 1 (vs. no exacerbations) OR [95% CI]	1.040 [0.614–1.761] (p = 0.147)	1.005 [0.966–1.045] (p = 0.819)
High dose of ICS (vs. low/medium doses) OR [95% CI]	**1.416 [1.187–1.925] (p = 0.031)**	1.171 [0.977–1.226] (p = 0.105)
SABA use > 1 (vs. no use) OR [95% CI]	1.368 [0.596–3.137] (p = 0.459)	1.018 [0.981–1.058] (p = 0.341)
Unchanged level or step-up of therapy (vs. step-down of treatment) OR [95% CI]	0.863 [0.426–1.749] (p = 0.682)	0.995 [0.964–1.027] (p = 0.749)

Note: Each box of the table represents a model. Logistic and regression models were applied considering the reversibility test results as dichotomous or as continue variables. Each line was a different model. Significant results are showed in bold. Each model was adjusted for age, FEV_1, BMI, various sensitisations, IgE value, Omalizumab dose, comorbidities (considering separately: hypertension, diabetes, rhinitis, sinusitis, nasal polyposis, chronic heart disease, osteoporosis, OSAS, mental disorders, gastroesophageal reflux),smoking habits, age of asthma onset, ICS dose, LABA use, Montelukast use, aspirin intolerance, eosinophils and short-acting bronchodilator response.

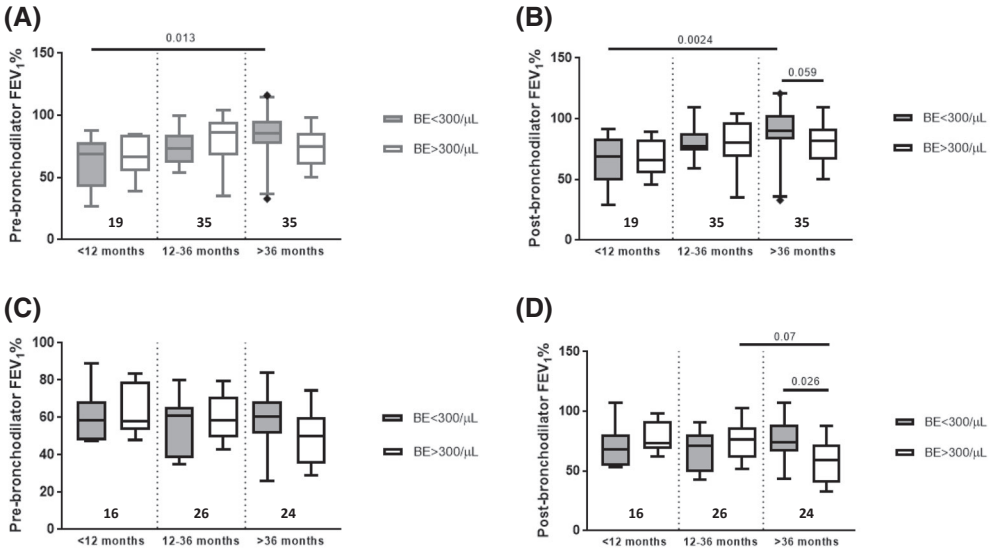

FIGURE 1 Pre- and post-bronchodilator FEV_1% measured at different times of step-5 asthma guidelines treatment in RAO− (A and B) and RAO+ subjects (C and D), related to blood eosinophil counts measured at the end of each patient's treatment period (grey box: blood eosinophil counts ≤300 cells/µl; white box: blood eosinophil counts > 300 cells/µl). The number of patients are shown under the box-plots

FEV_1% and ACT, confirming that RAO and worse lung function/asthma control were associated as observed, although in less severe asthmatics, by other studies.[1,2] Furthermore, such outcomes appeared to be related to the bronchodilator response magnitude. This significant relationship between bronchodilator reversibility and reduced FEV_1 and ACT outcomes confirms the importance of excessive airway narrowing in determining lung function impairment and consequently worse symptoms. Despite a step-5 level treatment, an association between bronchodilator reversibility and persistently

higher BE counts was also found, suggesting that eosinophilic airway inflammation may cause/influence excessive airway narrowing and consequently reduced outcomes. Other studies have confirmed an association between the reversible airflow and the eosinophilic pattern.[3–6] Furthermore, other researches assert that failing to reduce eosinophilic inflammation (BE and/or FENO) significantly influences asthma control and lung function improvement.[10,16,17] Hence, the reversibility test may be a marker of reduced response because it may reflect a persistent eosinophilic airway inflammation suggesting possible different treatments as anti-eosinophilic therapies.

RAO+ subjects showed a lower post-treatment FEV_1, confirming what observed by other studies.[5,6,8] Patients with significant reversibility may show an excessive airway narrowing due to airway smooth muscle contraction, very probably eosinophilic-inflammation induced. Actually, correlations between airway hyperresponsiveness and sputum eosinophils,[18] as well as BE counts, serum IgE levels and FENO concentrations in RAO asthmatics were found.[3–6] Eosinophilic inflammation markers were associated to lower baseline lung function.[3–6,18] When considering FEV_1 at different times of treatment, a progressive declining of pre/post-bronchodilator FEV_1% was detected only in subjects with a significant bronchodilator reversibility and not in RAO− asthmatics. This indicates that a persistent positive bronchodilator reversibility (despite treatments) may predict lung function decline. However, only when observing RAO+ subjects with persisting higher BE counts, we observed an accelerated lung function decline with a lower FEV_1% after more than 36 months of treatment in comparison to patients treated for a shorter period and to those with lower BE values. Conversely, in RAO− individuals with lower BE counts, even lung function improved over time. Therefore, lung function decline requires the association of a marked airway narrowing and eosinophilic inflammation. Studies have recently found an association between higher blood/sputum eosinophil counts and lung function decline among asthmatics,[8–13] which, according to our results, may affect approximately 23% of patients receiving a step-5 treatment associated with omalizumab. It is not clear how eosinophilic inflammation affects lung function decline. Eosinophils play an important role in asthma pathogenesis: they are promotors of the inflammatory response and directly and indirectly associated to airway remodelling. The cytotoxic proteins secreted by eosinophils can directly damage airway epithelial cells. Some authors have observed associations between airway remodelling and cellular inflammation with submucosal eosinophilia,[19] a marker (and probably cause) of epithelial damage related to airway smooth muscle (ASM) infiltration with eosinophils and T lymphocytes.[20] ASM layer increased thickness was connected with airway remodelling and eosinophilia.[21] Eosinophils produce further TGF β1, which promotes fibroblast proliferation, the maturation of myofibroblasts and collagen synthesis. They may also help direct angiogenesis in the asthmatics' submucosa by producing several angiogenetic factors, including VEGF.[22–24] It is possible that the elevated levels of eosinophils are actually induced by the high production of IL5 and that this cytokine may play a role in lung function decline. In fact, a recent study has shown the existence of an association between high levels not only of eosinophils but also of IL-5 (in induced sputum) and accelerated FEV_1 decline.[11] Anti-IL-5 treatment in asthma patients was associated with a significant reduction in the numbers of airway eosinophils expressing mRNA for TGF-β1 and the concentration of TGF-β1 in BAL fluid.[25] Furthermore, a 12-month treatment with anti-IL5 resulted in improvements in exacerbations, systemic and local eosinophil counts and reductions of the total airway area and of the airway wall area on CT, compared to findings in the placebo group.[26] Therefore, according to our results, bronchodilator reversibility identifies asthmatics with accelerated lung function decline (despite elevated treatment levels) only when associated to persistent eosinophilic airway inflammation. Consequently, bronchodilator reversibility test, together with BE measurements, should be considered in asthma management and not only to diagnose/phenotype the disease.

In conclusion, despite a maximal step-5 treatment, persistence of both SABA-induced bronchodilator reversibility and higher BE levels may be not only a sign of poor asthma control, but also a marker of accelerated lung function decline in severe allergic asthmatics. The main goal of asthma treatment should be achieving maximal bronchodilation associated to the lowest blood eosinophil levels to improve disease control and above all to prevent lung function decline. Further studies are needed to confirm these findings.

ACKNOWLEDGEMENTS

The Italian Omalizumab Study Group includes the following members: B. Sposato, M. G. Migliorini, M. Di Tomassi, C. Olivieri, A. Perrella (U.O.C. Pneumologia, Azienda USLSUDEST, Toscana, Ospedale 'Misericordia', Grosseto); G. Camiciottoli (Respiratory Unit, A. O. Careggi—Firenze); R. Maselli, G. Pelaia, M. T. Busceti (U.O.C. Pneumologia, Policlinico Universitario Mater Domini—Catanzaro); E. Sabato, M. G. Cagnazzo (U.O. Pneumologia, Ospedale Melli e San Pietro Vernotico—Brindisi); F. Colombo, L. Palumbo (U.O. Pneumologia, A.O. Ospedale di Circolo e Fondazione Macchi—Varese); A. Ravazzi (Ospedale Sant'Anna—Como); C. Bucca (S.C. Pneumologia, A.O. Città della Salute e della Scienza—Torino); M. F. Caiaffa (U.O. Allergologia e Immunologia Clinica, A.O.U. Ospedali Riuniti—Foggia); A. Berra (SSD Allergologia Respiratoria, Ospedale Giovanni da Procida—Salerno); C. Calabrese (U.O.C. Clinica Pneumologia Sun, Ospedale Monaldi—Napoli); A. A. Stanziola (U.O.C.

Pneumotisiologia 1, Ospedale Monaldi—Napoli); P. Schino (U.O.S. Fisiopatologia Respiratoria, Ospedale Miulli, Acquaviva delle Fonti—Bari); M. Di Gioacchino (U.O. Allergologia e Immunologia Clinica, Ospedale SS Annunziata—Chieti); P. Rogliani, M. Cazzola, A. Segreti (U.O.C. Malattie Apparato Respiratorio, Policlinico Tor Vergata—Roma); E. A. Pastorello, G. Scibilia (Dipartimento Allergologia e Immunologia, A.O. Ospedale Niguarda Ca' Grande—Milano); A. Vianello, M. R. Marchi, L. Paladini (U.O.C. Fisiopatologia Respiratoria, A.O. di Padova); S. Baglioni, M. Abbritti (U.O. Pneumologia e Unità di Terapia Intensiva, A.O. di Perugia); F. Almerigogna, A. Matucci, A. Vultaggio (SOD Immunoallergologia, A.O.U. Careggi, Firenze); E. Maggi (SOD Immunologia e Terapie Cellulari, A.O.U. Careggi, Firenze); P. Maestrelli, G. Guarnieri (U.O.C. Medicina del Lavoro, A.O. di Padova); G. Steinhilber (U.O. Pneumologia e Fisiopatologia Respiratoria, A.O. Spedali Civili—Brescia); M. Bonavia (U.O. Pneumologia, Ospedale La Colletta—Genova); P. Rottoli, E. Bargagli (U.O. Malattie Respiratorie e Trapianto Polmonare, A.O.U. Siena); G. Senna, M. Caminati (U.O. Allergologia, A.O.U. Verona); L. Macchia (Unità Dipartimentale di Allergologia e Immunologia Clinica, A.O.U. Policlinico Bari); V. Bellia, N. Scichilone (U.O. Malattie apparato Respiratorio 2, A.O. Ospedali Riuniti Villa Sofia-Cervello—Palermo); P. Paggiaro, F. Novelli, M. Latorre, L. Vergura (Sez. Dip. Fisiopatologia Respiratoria e Riabilitazione Respiratoria, A.O.U. Pisana); S. Masieri (Clinica Otorinolaringoiatrica, Poli-clinico Umberto I, Università di Roma 'Sapienza'); M. Scalese (Istituto di Fisiologia Clinica, CNR, Pisa); Y. Rosati (Pneumologia, Ospedale di Macerata); M. Milanese (Pneumologia, Ospedale S.Corona, Pietra Ligure); I. Folletti (Sezione di Medicina del Lavoro, Malattie Respiratorie e Tossicologia Professionale ed Ambientale, Dipartimento di Medicina, Università di Perugia, Az. Ospedaliera Santa Maria, Terni); R. Pio, A. Pio (Allergologia e Immunologia Clinica, Ospedale G. Fucito e Mercato S. Severino, Salerno); U. Maccari, C. Maggiorelli, R. Scala (Pneumologia e UTIP, Ospedale 'S.Donato', Arezzo); L. Vignale (Pneumologia, Ospedale di Fivizzano); N. Pulerà (Pneumologia, Ospedale di Livorno); G. E. Carpagnano, M. P. Foschino Barbaro (Institute of Respiratory Disease, Department of Medical and Occupational Sciences, University of Foggia, Italy).

CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest with the contents of this article.

AUTHOR CONTRIBUTIONS

Bruno Sposato was involved in study design and manuscript writing as the overall study principal investigator. Marco Scalese performed the statistical analysis. Alberto Ricci, Paola Rogliani and Pierluigi Paggiaro contributed to sample preparation. All authors discussed the results and contributed to the final manuscript.

DATA AVAILABILITY STATEMENT

Data of this study are not available to sharing as participants were informed that data management would be controlled only by authors at all times.

ETHICS

Data concerning individuals enrolled for the Novelli et al study,[15] for which the protocol was approved by Pisa University Hospital's Ethics Committee, (protocol 105 FPR0001 no. 3436, approved on 10 November 2011) and for which informed consent was obtained for each patient, was used for the purpose of our study. Post hoc analysis of the previous study's data was performed according to the objective of our research. All evaluations were conducted in compliance with the Declaration of Helsinki.

ORCID

Bruno Sposato https://orcid.org/0000-0003-4439-7209

REFERENCES

1. Heffler E, Crimi C, Campisi R, et al. Bronchodilator response as a marker of poor asthma control. *Respir Med*. 2016;112:45-50.
2. Coverstone AM, Bacharier LB, Wilson BS, et al. Clinical significance of the bronchodilator response in children with severe asthma. *Pediatr Pulmonol*. 2019;54:1694-1703.
3. Smith RW, Downey K, Snow N, et al. Association between fraction of exhaled nitrous oxide, bronchodilator response and inhaled corticosteroid type. *Can Respir J*. 2015;22:153-156.
4. Faul JL, Demers EA, Burke CM, et al. Alterations in airway inflammation and lung function during corticosteroid therapy for atopic asthma. *Chest*. 2002;121(5):1414-1420.
5. Busse WW, Holgate ST, Wenzel SW, et al. Biomarker profiles in asthma with high vs low airway reversibility and poor disease control. *Chest*. 2015;148:1489-1496.
6. Chou K-T, Su K-C, Hsiao Y-H, et al. Post-bronchodilator reversibility of FEV1 and eosinophilic airway inflammation in COPD. *Arch Bronconeumol*. 2017;53:547-553.
7. Wei J, Ma L, Wang J, et al. Airway reversibility in asthma and phenotypes of Th2-biomarkers, lung function and disease control. *Allergy Asthma Clin Immunol*. 2018;14:89.
8. Hancox RJ, Pavord ID, Sears MR. Associations between blood eosinophils and decline in lung function among adults with and without asthma. *Eur Respir J*. 2018;51:1702536.
9. Coumou H, Westerhof GA, de Nijs SB, et al. Predictors of accelerated decline in lung function in adult-onset asthma. *Eur Respir J*. 2018;51:1701785.
10. Graff S, Demarche S, Henket M, et al. Increase in blood eosinophils during follow-up is associated with lung function decline in adult asthma. *Respir Med*. 2019;152:60-66.
11. Marc-Malovrh M, Camlek L, Škrgat S, et al. Elevated eosinophils, IL5 and IL8 in induced sputum in asthma patients with accelerated FEV1 decline. *Respir Med*. 2020;162:105875.

12. Backman H, Lindberg A, Hedman L, et al. FEV1 decline in relation to blood eosinophils and neutrophils in a population-based asthma cohort. *World Allergy Organ J*. 2020;13:100110.
13. Mogensen I, Vonk JM, Wijnant SRA, et al. Blood eosinophil level and lung function trajectories: cross-sectional and longitudinal studies in European cohorts. *ERJ Open Res*. 2020;6: 00320-2020.
14. Sposato B. Could FEV_1 decline have a role in daily clinical practice for asthma monitoring? *Curr Med Res Opin*. 2013;29: 1371-1381.
15. Novelli F, Latorre M, Vergura L, et al. Asthma control in severe asthmatics under treatment with omalizumab: a cross-sectional observational study in Italy. *Pulm Pharmacol Ther*. 2015;31: 123-129.
16. Sposato B, Scalese M, Milanese M, et al. Omalizumab Italian Study Group. Higher blood eosinophil levels after omalizumab treatment may be associated with poorer asthma outcomes. *J Allergy Clin Immunol Pract*. 2019;7:1643-1646.
17. Oishi K, Hirano T, Suetake R, et al. A trial of oral corticosteroids for persistent systemic and airway inflammation in severe asthma. *Immun Inflamm Dis*. 2017;5:261-264.
18. Hara J, Fujimura M, Myou S, et al. Sputum eosinophilia, airway hyperresponsiveness and airway narrowing in young adults with former asthma. *Allergol Int*. 2008;57:211-217.
19. Kuo CS, Pavlidis S, Zhu J, et al. Contribution of airway eosinophils in airway wall remodeling in asthma: role of MMP-10 and MET. *Allergy*. 2019;74:1102-1112.
20. Wilson SJ, Rigden HM, Ward JA, et al. The relationship between eosinophilia and airway remodelling in mild asthma. *Clin Exp Allergy*. 2013;43:1342-1350.
21. Elliot JG, Jones RL, Abramson MJ, et al. Distribution of airway smooth muscle remodelling in asthma: relation to airway inflammation. *Respirology*. 2015;20:66-72.
22. Chetta A, Zanini A, Foresi A, et al. Vascular endothelial growth factor up-regulation and bronchial wall remodelling in asthma. *Clin Exp Allergy*. 2005;35:1437-1442.
23. Halwani R, Al-Muhsen S, Al-Jahdali H, Hamid Q. Role of transforming growth factor-β in airway remodeling in asthma. *Am J Respir Cell Mol Biol*. 2011;44:127-133.
24. Hoshino M, Takahashi M, Aoike N. Expression of vascular endothelial growth factor, basic fibroblast growth factor, and angiogenin immunoreactivity in asthmatic airways and its relationship to angiogenesis. *J Allergy Clin Immunol*. 2001;107:295-301.
25. Flood-Page P, Menzies-Gow A, Phipps S, et al. Anti-IL-5 treatment reduces deposition of ECM proteins in the bronchial subepithelial basement membrane of mild atopic asthmatics. *J Clin Invest*. 2003;112:1029-1036.
26. Haldar P, Brightling CE, Singapuri A, et al. Outcomes after cessation of mepolizumab therapy in severe eosinophilic asthma: a 12-month follow-up analysis. *J Allergy Clin Immunol*. 2014;133:921-923.

How to cite this article: Sposato B, Scalese M, Ricci A, Rogliani P, Paggiaro P; The Omalizumab Italian Study Group. Persistence of both reversible airway obstruction and higher blood eosinophils may predict lung function decline in severe asthma. *Clin Respir J*. 2021;15:237–243. https://doi.org/10.1111/crj.13325